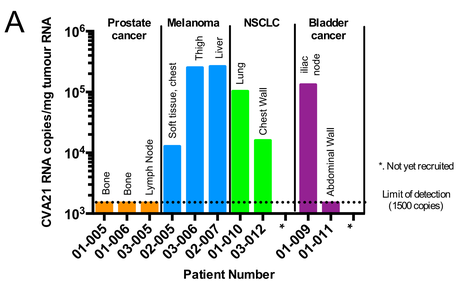
# #TPS3108: Phase I STORM study *(KEYNOTE 200)*: Intravenous delivery of a novel oncolytic immunotherapy agent, Coxsackievirus A21 in combination with pembrolizumab in advanced cancer patients.

Hardev S. Pandha[1], Kevin J. Harrington[2], Christy Ralph[3], Alan Melcher[2], Brendan Curti[4], Rachel Sanborn[4], David Mansfield[2], Emmett Schmidt[5], David Kaufman[5], Mark Grose[6], Bronwyn Davies[6], Roberta Karpathy[6], Darren Shafren[6]

*[1] University of Surrey, Surrey, UK; [2] Institute of Cancer Research and Royal Marsden Hospital, London, UK; [3] Institute of Oncology, St. James's University Hospital, Leeds, UK; [4]Providence Cancer Center, Portland, OR; [5]Merck & Co., Inc., Kenilworth, NJ; [6]Viralytics Limited, Sydney, Australia*

## Background

Coxsackievirus A21 (CVA21, CAVATAK) is a naturally occurring ICAM-1 targeted oncolytic immunotherapeutic virus. Intravenous (IV) delivery of CVA21 targets various systemic solid tumors (*Figure 1*). Tumor infection by CVA21 can increase levels immune-checkpoint molecules, immune-cell infiltration and enhancement of systemic antitumor immune response. Pembrolizumab is a human programmed death receptor-1 (PD-1) blocking antibody that has yielded significant solid tumor responses via reversal of tumor induced T-cell suppression. Preclinical studies in an immune-competent mouse model of Non-Small Cell Lung Cancer (NSCLC) confirmed that combinations of IV CVA21 + anti-PD-1 mAbs mediated survival benefit compared to use of either agent alone (*Figure 2*). We postulate that the combination of CVA21+pembrolizumab may translate to a similar benefit in the clinic. We describe a Phase I study assessing safety and efficacy of IV CVA21 ± pembrolizumab in advanced cancer patients.



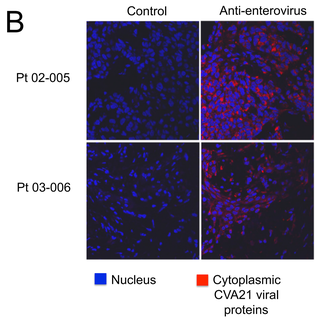




***Figure 1. Phase I KEYNOTE 200 study: CVA21 tumor targeting. (A) CVA21 detection by qRT-PCR in tumor biopsies (Part A) at study day 8 and (B) IHC detection of active CVA21 replication at study day 8 in tumor biopsies from 2 patients (Part A) with advanced melanoma following 3 intravenous infusions of CVA21 ($10^9 TCID_{50}$/infusion).***

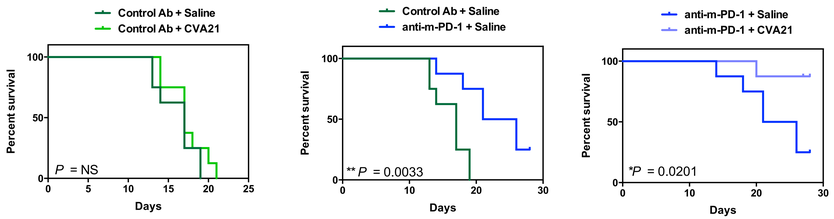
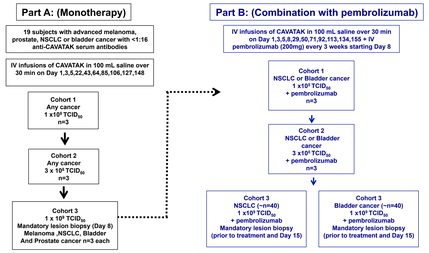



***Figure 2. Kaplan-Meier Survival analysis: Combination of intravenous CVA21 and intraperitoneal anti-murine-PD-1 monoclonal antibody in an immune-competent C57BL mouse model of NSCLC (3LL-hICAM-1) (n=8).***

## Study Design




## Study Treatment

***Part A:*** Pts are infused with CVA21 in 100 mL saline in Cohort 1 (n = 3), at a dose of 1 x $10^8$ $TCID_{50}$, in Cohort 2 (n = 3) at a dose of 3 x $10^8$ $TCID_{50}$ and in Cohort 3 (n = 12-18) at a dose of 1 x $10^9$ $TCID_{50}$ on study days 1,3,5,22 and Q3W for 6 additional infusions.
Part A enrollment is almost complete.

***Part B:*** Pts are infused with CVA21 in 100 mL saline + pembrolizumab. In Cohort 1 (n = 3), CVA21 is administered at a dose of 1 x $10^8$ $TCID_{50}$, in Cohort 2 (n = 3) at a dose of 3 x $10^8$ $TCID_{50}$ and in Cohort 3 (n = ~80) at a dose of 1 x $10^9$ $TCID_{50}$ on study days 1,3,5,8,29,and Q3W for 6 additional infusions. Pembrolizumab is given in all cohorts at 200 mg IV Q2W from Day 8 for up to 2 years. Treatment with CVA21 ± pembrolizumab will continue until confirmed CR or PD (whichever comes first) per irRECIST or DLT.

## Eligibility Criteria

**Key Inclusion criteria**

- *Part A:* Histologically-confirmed (1) NSCLC, (2) bladder cancer, (3) castrate-resistant prostate cancer (CRPC) which are metastatic, or (4) Stage IIIC or Stage IV melanoma.
- *Part B:* Histologically or cytologically-confirmed (1) advanced NSCLC, (2) urothelial carcinoma (also known as transitional cell carcinoma). Urothelial carcinomas with variant histologic differentiation (e.g. squamous cell differentiation, glandular differentiation, neuroendocrine differentiation) will be eligible provided that the predominant histology is urothelial carcinoma.
- *Part B:* Patients with advanced disease who are considered candidates for protocol specified pembrolizumab to be used in combination with CVA21.
- *Part A:* All subjects in Cohort 3 or P2D cohort must have a lesion accessible for FNA or core biopsy or open biopsy on Day 8 of the first treatment cycle.
- *Part B:* All subjects in Cohort 3 or P2D cohort must have a lesion accessible for mandatory core biopsy or open biopsy prior to treatment and on Day 15 of the first treatment cycle. FNA is not acceptable for *Part B*.
- ECOG Performance Scale 0-1.
- Life expectancy >3 months.
- Measureable disease based on RECIST 1.1 as determined by the site study team. Tumour lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

**Key Exclusion criteria**

- Active cardiac disease: unstable angina or onset of angina within last 3 months, myocardial infarction within 6 months, congestive heart failure > class II, cardiac ventricular arrhythmias requiring anti-arrhythmic therapy.
- Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.
- Known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies), known active Hepatitis B (e.g. HBsAg reactive) or Hepatitis C (e.g. HCV RNA [qualitative] is detected).
- Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
- Known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.
- Active infection requiring systemic therapy.
- Has had prior anti-cancer monoclonal antibody within 21 days prior to Study Day 1 or who has not recovered (i.e. ≤ Grade 1) from adverse events due to agents administered more than 21 days earlier.
- Has known active central nervous system metastases and/or carcinomatous meningitis.

## Study Objectives

**Primary Objectives**

*Part A:*

- To determine if CVA21 given intravenously is capable of tracking to malignant tumours
- To establish a safe dose schedule of CVA21 to take into subsequent Phase 2 clinical trials.
- To describe the safety profile for intravenously-administered CVA21.

*Part B*

- To assess the safety and efficacy of intravenous CVA21 and intravenous pembrolizumab in solid tumours of metastatic bladder cancer and non-small cell lung cancer.
- To identify a safe and potentially effective Phase 2 dose for CVA21 in combination with intravenous pembrolizumab.
- To investigate if intravenous CVA21 when given in combination with intravenous pembrolizumab is capable of tracking to remote tumour sites by exhibiting CVA21 RNA in metastatic lesions at biopsy.
- To determine if CVA21 in combination with intravenous pembrolizumab is capable of replicating in the tracked tumour sites leading to tumour cell lysis while sparing the surrounding normal cells.

**Secondary Objectives**

*Part B*

- To assess efficacy via RECIST 1.1 and immune-related RECIST (irRECIST) criteria.
- To correlate ICAM-1 expressivity and DAF expressivity with the ability of CVA21 to reach its target and replicate within tumour cells.
- To assess immune response (e.g. immune cell infiltrates) after the first course of CVA21 via biopsy of an accessible tumour lesion.
- To assess tolerance to intravenous CVA21 for up to 8 courses (21 day cycle) in combination with pembrolizumab.
- To assess the PK/PD of CVA21 as measured by CVA21 RNA in serum over time.
- Other studies in the post-treatment biopsy specimen and blood samples, including studies for TH1 cytokine inflammatory response, cellular inflammatory response, evidence for viral infection and replication for target tumour and no replication in normal tissue, and exploratory biomarkers of immune response including, but not limited to, PD-L1 expression.
- Effect of pembrolizumab on the expected humoral response to CVA21.
- CVA21 excretion and shedding studies to assess environmental safety.

Viralytics
Developers of Oncolytic Immunotherapies

**Acknowledgement**

**Support for this study was provided by Viralytics Limited and Merck & Co., Inc.**

Copies of this poster obtained through Quick Response (QR) Code are for personal use only and may not be reproduced without permission from ASCO and the author of this poster.

 *Corresponding author: Hardev Pandha h.pandha@surrey.ac.uk*